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Indices of acceleration atelectasis and the effect of hypergravity duration on its development

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Abstract

Recently, there have been reports of acceleration atelectasis during fast jet flight despite the use of systems designed to minimize this. Before further investigation of this, indices suitable for use in applied settings and identification of acceleration durations that elicit it are required.

Fifteen non-aircrew subjects underwented five centrifuge exposures lasting 15, 30, 60 and 2×90 s with a plateau of +5 Gz (acceleration in the cranial-caudal direction) while breathing 94% O_2 during all but one control exposure (21% O_2). Lung volumes and gas exchange limitation were assessed after each exposure. Regional lung impedance and compliance were measured after Gz exposure using electrical impedance tomography and the forced oscillatory technique, respectively.

The presence of acceleration atelectasis was confirmed by reductions of 10–17% in vital and inspiratory capacity after 60 and 90 s Gz exposures ($P < 0.05$) and resulted in reduced regional lung impedance and a gas exchange limitation of 8.1 and 12.5%, respectively ($P < 0.05$). There was also a small but significant decrease in regional lung impedance after 30 s exposures. Functional residual capacity and lung compliance were unchanged in atelectatic lungs ($P > 0.05$).

In the majority of individuals, >60 s of Gz exposure while breathing 94% O_2 causes acceleration atelectasis. Electrical impedance tomography and the measurement of gas exchange limitation provide useful indicators of acceleration atelectasis. Acceleration atelectasis exerts its effects primarily through basal lung closure and reflex inspiratory limitation, both of which can be reversed by performing three maximal inspiratory breathing manoeuvres.

KEYWORDS
centrifuge, electrical impedance tomography, forced inspiratory vital capacity, hyperoxia, pulmonary shunt

1 | INTRODUCTION

During the 1960s, radiographic examination of combat jet pilots reporting respiratory complaints (e.g. cough, chest pain, breathing difficulties) during or after flight revealed the presence of atelectasis (Green & Burgess, 1962; Levy, Jaeger, Stone, & Doudna, 1962), a partial collapse of lung tissue impairing gas exchange. The condition became known as acceleration, or aero-, atelectasis and occurred during exposure to +Gz acceleration (cranial–caudal direction) when combined with breathing gas mixtures containing high oxygen concentrations when wearing anti-G trousers (AGT) (Hyde, Pines, & Saito, 1963). The causative mechanism of this condition is basal airway closure, attributable to compression of lower lung regions by +Gz-induced intrapleural pressure increases and AGT abdominal bladder inflation, with subsequent gas absorption rendering unventilated alveoli atelectatic.

It is typically assumed that breathing a gas mixture containing <60% oxygen will prevent acceleration atelectasis owing to the slower rate of gas absorption associated with greater nitrogen and, consequently, lower oxygen concentrations (Ernsting, 1965). This threshold was determined from research investigating levels of acceleration associated with legacy aircraft and anti-G systems. Recently, there have been anecdotal reports of the development of acceleration atelectasis in fast jet pilots (Monberg, 2013) despite the use of on-board oxygen generation systems that should adhere to oxygen schedules limiting the maximal oxygen concentration to 60%, suggesting that this limit might no longer be valid. This might be attributable to the capabilities of modern aircraft permitting different G-profiles at different altitudes compared with those used for the original research (Haswell, Tacker, Balldin, & Burton, 1986; Tacker et al., 1987) and the greater use of anti-G systems involving full coverage (FCAGT) which, in contrast to partial coverage AGT, are likely to provide greater abdominal compression. Also, it is possible that on-board oxygen generation systems might supply excessive inspired O_2 concentrations (F_{I,O_2}) for the altitude flown (Borges et al., 2015; Monberg, 2013).

To determine why acceleration atelectasis might be developing, despite the use of previously effective mitigation strategies, further research is required. Initially, this requires identification of protocols that can elicit it. Whilst acknowledging an effect of the magnitude of acceleration and the oxygen concentration, there is no clear consensus on the duration of +Gz exposure required for its development, with symptoms being reported after exposures lasting between 15 and 180 s (Borges et al., 2015; Glaister, 1965; Haswell et al., 1986; Hyde et al., 1963). The longer the duration of +Gz exposure, the greater the length of time for which basal airways will be closed and alveoli unventilated. Subsequently, owing to the marked increase in the rate of gas absorption from unventilated alveoli when breathing hyperoxic gas mixtures (Dale & Rahn, 1952), pulmonary vascular engorgement (Rohdin & Linnarsson, 2002) and preferential distribution of perfusion to lower lung regions under +Gz (von Nielding, Krekeler, Koppenhagen, & Ruff, 1973), the greater the likelihood of alveolar collapse. The time required for this is an important consideration, because operational exposures to +Gz are usually much shorter than those used in laboratory studies, where it is possible that exposures of 15–30 s might cause atelectasis (Glaister, 1965), although this has yet to be demonstrated empirically.

Given the development of acceleration atelectasis during high Gz acceleration exposures and the likelihood of its reversal on exiting an aircraft, it remains a challenging condition to assess. The clinical gold-standard measure of atelectasis is high-resolution computed tomography (Hedenstierna, 2000), but it is not practical to perform this during or immediately post-flight (or centrifugation). A surrogate measure that is the most commonly used to assess acceleration atelectasis, forced inspiratory vital capacity (FIVC), overcomes this limitation, but the manoeuvre itself acts to reverse atelectasis; therefore, identification of alternative methods to assess acceleration atelectasis are required. In this regard, electrical impedance tomography (EIT), which allows real-time imaging of the

New Findings

- **What is the central question of the study?**
  The aim was to determine the effects of duration of acceleration in the cranial–caudal direction (+Gz) on acceleration atelectasis and identify measurement techniques that can be used to assess it.

- **What is the main finding and its importance?**
  Non-invasive measurement of acceleration atelectasis using electrical impedance tomography and estimates of pulmonary shunt provide more detailed assessment of acceleration atelectasis than traditional forced vital capacity measures. Using these techniques, it was found that as little as 30 s of exposure to +Gz acceleration can cause acceleration atelectasis. The results of the present study will allow a more accurate and detailed assessment of acceleration atelectasis in the future.

lung and measurement of the changes in impedance across the lung, could be a promising technique to study acceleration atelectasis and has recently been used for this purpose (Borges et al., 2015). Another technique that has been used to quantify atelectasis is the forced oscillatory technique (Dellaca et al., 2009), which allows determination of lung resistance, reactance and compliance (Pride, 1992), although it has never been used for this purpose in humans. Finally, if an individual had become atelectatic, a pulmonary shunt and/or ventilation–perfusion mismatch would be expected. Therefore, it might be possible to assess the extent of acceleration atelectasis via non-invasive measurement of these (Kjaergaard et al., 2003; Lockwood, Fung, & Jones, 2014; Sapsford & Jones, 1995) using a technique that could be applied in aviation-relevant settings.

The aims of the study were as follows: (i) to investigate measurement techniques that can be used as surrogate measures of acceleration atelectasis; and (ii) to determine the duration of +Gz exposure required for acceleration atelectasis to develop (while breathing a 94% O_2 gas mixture). With regard to the duration of acceleration that can elicit atelectasis, it was hypothesized that ≥30 s exposures to acceleration would be required for its development.

2 | METHODS

2.1 | Ethical approval

All procedures detailed in the manuscript were approved by the UK Ministry of Defence Research Ethics Committee (696/MoDREC/15). All subjects provided written informed consent before participation. The study protocol adhered to the principles of the *Declaration of Helsinki* except for registration in a database.

Thirteen male and two female non-aircrew participants (mean ± 1SD: age, 28 ± 7 years; body mass, 82 ± 12 kg; and height,
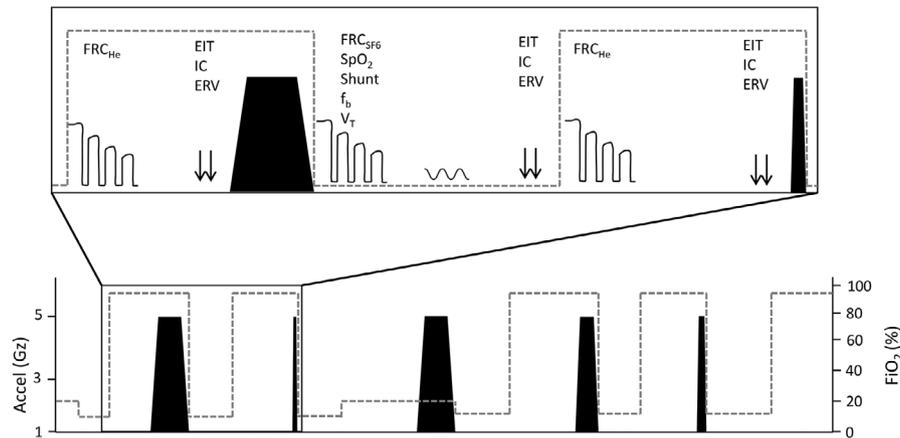
FIGURE 1 Graphical representation of the experimental protocol and the points at which each measurement was made. Filled black regions represent periods of Gz (acceleration in the cranial-caudal direction) exposure (the order of durations was determined randomly). The dashed grey line indicates the inspired oxygen concentration (F_{I,O_2}). The stepped black line indicates periods when inert gas washout was performed, and the sine wave represents the forced oscillatory technique period. Downward arrows indicate the points at which forced inspiratory vital capacity manoeuvres were performed. Abbreviations: EIT, electrical impedance tomography; ERV, expiratory reserve volume; f_b, breathing frequency; FRC, functional residual capacity; IC, inspiratory capacity; S_{pO_2}, peripheral oxygen saturation; V_T, tidal volume

179 ± 8 cm), trained up to +9 Gz on the centrifuge, completed the study. All participants underwent medical screening that included 12-lead ECG and echocardiography. Any individual >40 years of age or with a history of smoking, asthma or cardiovascular disease, was excluded.

2.2 | Set-up and procedure

Each subject made two visits to a human-rated long-arm (9.14 m radius) centrifuge facility (Farnborough, UK). During the first visit, subjects were familiarized with the experimental set-up. For the second experimental session, subjects were harnessed into an aircraft ejection seat reclined 23 deg from the vertical (10B-2 Mk1; Martin Baker Aircraft Company Ltd, Higher Denham, Middlesex, UK) and wore an aircrew coverall, inflatable sock bladders, a flight jacket, FCAGT and a purpose-built helmet and mask assembly. All equipment was fitted by a qualified survival equipment specialist. During the trial, the FCAGTs began to inflate at +2 Gz, with the pressure increasing linearly by 10 kPa G^{-1} (Aircrew Service Package, Honeywell Aerospace, Yeovil, UK). Breathing gasses were delivered without pressure from an independent demand valve regulator. The test schedule consisted of a total of five acceleration exposures at +5 Gz achieved using onset/offset rates of 1 G s^{-1}. This level of +Gz was expected to elicit acceleration atelectasis while being sufficiently low that subjects would not have to perform the breathing component of the anti-G straining manoeuvre, which has been shown to have a preventative effect on the development of acceleration atelectasis (Tacker et al., 1987). Four of these exposures, lasting 15, 30, 60 and 90 s, were undertaken with the subject breathing a hyperoxic gas mix [94% O_2, 6% sulphur hexafluoride (SF_6)] known to be sufficient to cause acceleration atelectasis. The remaining acceleration exposure lasted 90 s and was undertaken with the subject breathing a normoxic gas mix (21% O_2, 5% SF_6, balance N_2) which should prevent acceleration atelectasis from developing. The order of +Gz

exposures was randomized. Subjects were permitted to perform lower-body muscle tensing under +Gz in response to visual loss but were instructed to avoid the use of the breathing component of the anti-G straining manoeuvre. They were also asked to refrain from taking deep breaths and coughing whenever possible.

To assess the development of acceleration atelectasis, several measurement techniques were performed before and after acceleration exposure. These included measurement of the subject's FIVC, functional residual capacity (FRC), lung impedance, respiratory resistance, reactance and compliance, and pulmonary shunt. Details of each of these measurement techniques are given in the following sections.

Figure 1 provides an overview of the experimental procedure. Subjects initially breathed from a normoxic gas mixture until the end-tidal concentration of SF_6 stabilized (measured by respiratory mass spectrometer). The subjects then expired to their normal end-expiratory level, at which point the breathing gas was switched to a hypoxic gas mix (14% O_2, 5% He, balance N_2). The washout of SF_6 was used to compute FRC_{SF_6}, and the reduced F_{I,O_2} was designed to produce a mild hypoxaemia that would be more pronounced if gas exchange was impaired. Once the SF_6 had been washed out from the lungs, sinusoidal pressure oscillations were applied to the oronasal mask over a 30 s period, during which the respiratory compliance, reactance and resistance were measured using the forced oscillatory technique. Two FIVC manoeuvres (separated by ~30 s; FIVC 1 and 2) were subsequently performed, during which measures of regional lung volume were acquired using electrical impedance tomography (EIT); these occurred ~7 min after the end of the Gz exposure. Subjects then breathed out to their normal end-expiratory level, at which point the breathing supply was switched to that inspired under +Gz, which was either the hyperoxic (four runs) or normoxic (one run) gas. The washout of He provided a second FRC measurement (FRC_{He}) before the subject executed two further FIVC manoeuvres (FIVC 3 and 4). The +Gz exposure commenced when these measures were

complete and a stable end-tidal O_2 concentration (F_{ET,O_2}) had been reached. After this, before the Gz exposures, subjects were asked whether they had experienced chest tightness, shortness of breath or urge to cough during the previous Gz exposure or measurements. The above processes were repeated after each +Gz exposure. Participants remained seated in the centrifuge throughout testing.

2.3 | Measurements

2.3.1 | Functional residual capacity

Preliminary testing revealed that large changes in viscosity during washout of the hyperoxic gas coupled with the length of the mass spectrometer (MSX671; Ferraris Respiratory Europe Ltd., Hertford, UK) capillary ($\sim$15 m) resulted in significant variations in transit time and marked inaccuracies in FRC measurement. Therefore, a modified calculation of FRC measurement was used (Brewer, Orr, Sherman, Fulcher, & Markewitz, 2011). Briefly, the cumulative expired volume during the washout was recorded by integrating the expired flow rate (heated Fleisch pneumotachograph No. 2 connected to a differential pressure transducer; PSE550 series; SMC, Yorba Linda, California, USA) and plotted against the natural logarithm of the end-tidal SF_6 (or He) concentration on a breath-by-breath basis. The slope of the linear regression through these points reflects the size of the FRC, with smaller gradients indicating a larger FRC and vice versa. During the familiarization session, the reproducibility of FRC measurements was 10%, which is in agreement with recommended within-session FRC repeatability criteria (Robinson et al., 2013). To account for the time delay in the respiratory gas, associated with the mass spectrometer capillary length of 15 m, and the flow measurements, on each day before testing, a bolus of known gas was delivered simultaneously to both measuring devices and the delay from delivery to recording time determined.

2.3.2 | Lung volume

Measures of lung volume were derived from the integrated flow signal. The recorded values of flow from the Fleisch pneumotachograph were corrected to account for changes in the viscosity of the breathing gases which, by design, changed throughout the experiment (Blumenfeld, Turney, & Cowlet, 1973; Turney & Blumenfeld, 1973). The FIVC manoeuvres were performed by asking the subject to exhale until they reached residual volume, followed by a maximal inspiration to their total lung capacity, with a reduction in FIVC of 0.5 l assumed to be representative of acceleration atelectasis (Hyde et al., 1963). Subsequently, inspiratory capacity (IC) and expiratory reserve volume (ERV) were determined from the difference in volume between the average end-expiratory level over three normal tidal breaths to that recorded at full inspiration or full expiration, respectively. Tidal volume (V_T) and breathing frequency (f_b) were recorded from 1 min averages using a peak detection algorithm available in the data-acquisition software, with minute volume ($\dot{V}_E$) computed from these.

Basal lung volumes were quantified using EIT (Sheffield Mk 3.5 EIT system; Maltron, Rainham, UK), where eight electrodes were placed equidistantly around the circumference of the thorax at the level of the xiphoid process. A single reference electrode was placed over the anterior superior iliac spine. A current was applied between pairs of electrodes in a rotating sequence at 30 frequencies (2 kHz to 1.6 MHz) in three sequentially applied 'packets', each containing 10 frequencies with a root mean square amplitude of $\sim$212 μA. Purpose-built software (Matlab v.6.1; The Mathworks Inc., Natick, Massachusetts, USA) was used to acquire and process the resulting voltage measurements using a filtered back projection algorithm to form real-time images (sampling frequency, 25 Hz) of the lung consisting of 224 pixels. To derive a single value reflecting the change in impedance across the lung, pixel intensities were first represented as a percentage change from the intensity recorded at the subject's residual volume (measured pre-exposure). Then the image obtained at maximal inspiration was used to identify a region of interest to be applied to all subsequent analysis; this consisted of the 20 pixels (10 pixels in the left lung and 10 in the right) demonstrating the greatest variation in intensity (i.e. the point in each lung that had the greatest change in ventilation during the maximal inspiratory manoeuvre). For each measurement that was subsequently made, the average intensity in this region was used in computations of regional lung volume (rFIVC). The rFIVC was estimated as a relative (percentage) change in impedance from residual volume to maximal inspiration recorded during the FIVC.

2.3.3 | Respiratory compliance

Respiratory system compliance, resistance and reactance were measured using the forced oscillatory technique, whereby small amplitude (1–2 mmHg peak to peak) sinusoidal (5 Hz) pressure oscillations are applied to the respiratory tract and the resulting relationship between the airway pressure and volumetric flow rate at the frequencies of the forcing signal is assessed (MacLeod & Birch, 2001). To implement this, the data-acquisition system was used to provide a signal to an audio amplifier (Crown Amcron Macro Tech 1200 W; Crown Audio, Elkhart, Indiana, USA), which powered a 30.5 cm loudspeaker (3000 W, Space 12; Vibe Space, London, UK). A plate was placed over the cone of the loudspeaker to direct the pressure generated by its movement down a rigid plastic pipe of 9 mm internal diameter, which was connected directly to the mask assembly. The gain of the amplifier was adjusted to provide a 1–2 mmHg peak-to-peak pressure change.

Respiratory impedance, reactance and compliance were calculated using the method described by Bates, Irvin, Farré, and Zoltan (2011). Briefly, this involved determining the Fourier transforms of the pressure and flow signal, collected during three inspirations, and calculating the ratio of the two at the applied frequency. Respiratory reactance (X_{rs}) and resistance (R_{rs}) were obtained from the imaginary and real parts of the ratio, respectively. Respiratory compliance (C_{rs}) was computed as follows:

$$C_{rs} = \frac{1}{2\pi \times f \times X_{rs}}$$

where f represents the oscillatory frequency.

2.3.4 | Gas exchange limitation

An estimate of limitation in gas exchange, primarily pulmonary shunt and ventilation–perfusion mismatching, was made based on previously described techniques (Kjaergaard et al., 2003; Sapsford & Jones, 1995). The lowering of F_{I,O_2} during the hypoxic washout after +Gz exposure allowed a wide range of alveolar oxygen concentrations (from ~90 to 10%) and corresponding peripheral arterial oxygen saturations (S_{pO_2}) to be measured. The S_{pO_2} was measured by pulse oximetry (Radical 7 pulse oximeter; Masimo Corporation, Irvine, California, USA) at the ear lobe, with the time delay of the measurement system corrected by identifying the delay from when the breathing gas was switched from the hypoxic to hyperoxic mixture to a response being observed in S_{pO_2}. Alveolar oxygen tensions were estimated from end-expiratory oxygen concentrations (F_{ET,O_2}). These data recorded during the washout period were modelled, using a non-linear least-squares method, to a biexponential of the form:

$$S_{pO_2} = a \times e^{b \times F_{ET,O_2}} + c \times e^{d \times F_{ET,O_2}}$$

To quantify these data, a method was used in which the degree of gas exchange limitation was estimated for each subject by comparing the obtained curve (S_{pO_2} versus F_{ET,O_2}) with a series of similar curves generated (curves representing from 1 to 30% shunt, increasing in 1% increments) from an established mathematical model of gas exchange, in which the degree of shunt present was increased incrementally (Olzowka & Wagner, 1980); the shunt fraction of the generated curve that most closely resembled the recorded curve was taken as the shunt fraction. This method was chosen because it is anticipated that one of the primary effects of atelectasis would be the development of a significant level of pulmonary shunt, as previously reported (Green, 1963b). This technique could be performed only during hypoxic periods when sufficient ranges of F_{I,O_2} were experienced, i.e. immediately after hyperoxic Gz exposures. In addition, the lowest S_{pO_2} (min S_{pO_2}) value recorded during the hypoxic period was determined.

Analog-to-digital conversion of all measures was performed using a PC-based data-acquisition system (Powerlab 16SP; ADInstruments, Sydney, Australia) and recorded continuously on chart software (LabChart v.7; ADInstruments, UK).

2.4 | Statistical analysis

The Shapiro–Wilks test was applied to the dependent variables to assess distribution normality. The effect of the duration of Gz exposure on each variable was assessed using one-way repeated-measures ANOVA or, if not normally distributed, Friedman's test. If a significant main effect was found, planned contrasts were performed, where each post Gz exposure was compared against baseline values, with the exception of the level of pulmonary shunt, for which data recorded after the 15 s exposure were used (because insufficient F_{I,O_2} ranges were used to allow the shunt to be estimated from the baseline conditions). The first FIVC performed after each exposure was used to determine whether acceleration atelectasis had developed. To determine whether lung volume could be returned to normal with repeated maximal inspirations, the four FIVCs performed after each Gz exposure were assessed using one-way repeated-measures ANOVA. If a significant main effect was found, planned contrasts, in which each FIVC was compared against baseline FIVC, were performed. Statistical analysis was performed using IBM SPSS Statistics v.22 (Chicago, IL, USA) with significance set at $P < 0.05$. Data are presented as the mean value ($\pm$SD) unless otherwise indicated.

3 | RESULTS

One subject was withdrawn from the experiment after the third +Gz exposure after becoming lightheaded and not wishing to continue. In one subject after 60 and 90 s Gz (breathing 94% O_2) exposures, ~50 s of S_{pO_2} data were lost as a result of the probe detaching from the ear lobe under Gz. Finally, in one subject the EIT data recorded were of insufficient quality to be used for analysis owing to an electrode fault in the system.

An urge to cough was reported by zero, one, one, seven and one subjects after the 15, 30, 60, 90 (hyperoxic) and 90 s (normoxic) +Gz exposures, respectively. Symptoms related to chest tightness/shortness of breath were reported by one, one, three, five and zero subjects after the 15, 30, 60, 90 (hyperoxic) and 90 s (normoxic) +Gz exposures, respectively.

Based on measurements of FIVC, the development of acceleration atelectasis was dependent on the duration of prior +Gz exposure ($F_{2.06,26.78} = 9.74$, $P = 0.001$; Figure 2). When breathing 94% O_2 under +Gz, significant reductions in FIVC were noted after 60 ($P = 0.001$) and 90 s ($P = 0.005$) exposures, with no effect after 15 or 30 s ($P > 0.05$). After breathing 21% O_2 during a 90 s +Gz exposure, there was no change in FIVC compared with baseline ($P > 0.05$). When reductions in the first FIVC were found after +Gz exposure, this remained the case for the second ($P = 0.033$ and 0.044 for the 60 and 90 s exposure, respectively; Figure 2), although it had returned to baseline levels by the third and fourth ($P > 0.05$).

There was no measurable difference in FRC_{SF6} ($F_{5,65} = 1.457$, $P > 0.05$) or FRC_{He} ($\chi^2 = 1.62$, $P > 0.05$) after any duration of +Gz exposure (Table 1). A main effect of prior +Gz duration on IC (Table 1) was found ($F_{1.87,22.40} = 8.97$, $P = 0.002$), with significant declines after the 60 ($P = 0.001$) and 90 s (while breathing 94% O_2; $P = 0.003$) Gz exposures and a tendency towards this after the 30 s exposure ($P = 0.064$). The IC was unchanged after 15 (hyperoxic) and 90 s (normoxic) +Gz exposures ($P > 0.05$ in both cases). There was no effect of Gz duration, and therefore acceleration atelectasis, on ERV ($F_{5,60} = 0.799$, $P > 0.05$). A significant main effect of prior +Gz duration was found on V_T ($F_{5,65} = 3.56$, $P = 0.007$), with a greater V_T found only after the 90 s Gz exposure performed while breathing 21% O_2 ($P = 0.037$). A significant main effect of prior +Gz duration was also found on $\dot{V}_E$ ($F_{5,65} = 4.25$, $P = 0.002$), with a greater $\dot{V}_E$ found only after the 90 s Gz exposure performed while breathing 21% O_2 ($P = 0.035$).

There was a significant effect of prior +Gz duration on rFIVC ($F_{5,55} = 9.112$, $P < 0.001$; Figure 3). The rFIVC was significantly reduced after 30 ($P = 0.028$), 60 ($P = 0.004$) and 90 s ($P = 0.001$) hyperoxic
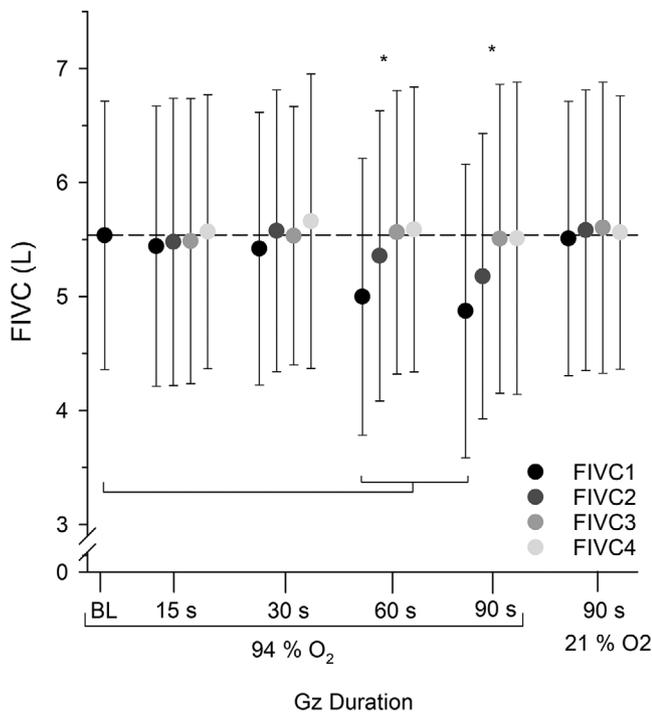
FIGURE 2 Mean (±SD) forced inspiratory vital capacity (FIVC) recorded after each duration of Gz (acceleration in the cranial-caudal direction) exposure and at baseline (BL). The oxygen concentration breathed before the hypoxic exposure during which measurements were made is shown. The bars presented below the data indicate a significant difference between the first FIVC and baseline ($P < 0.05$). *First and second FIVC are significantly ($P < 0.05$) lower than baseline (BL)
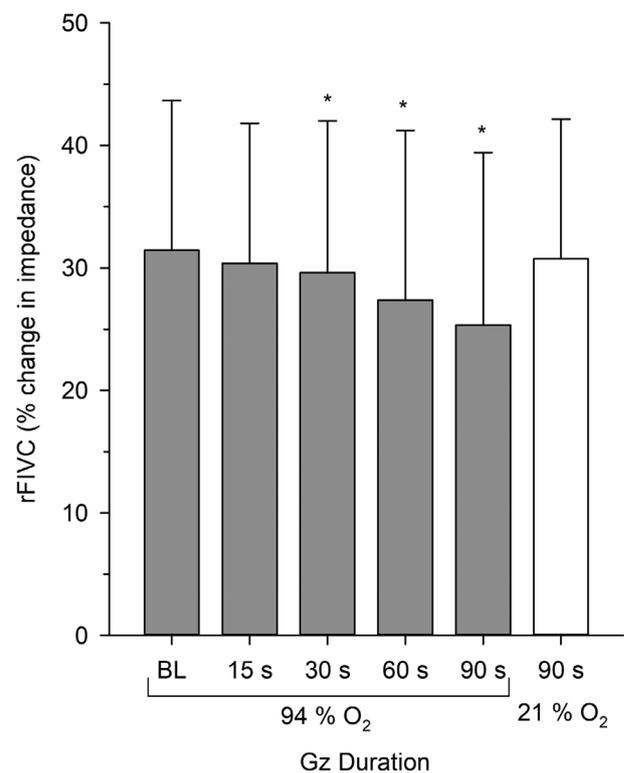

FIGURE 3 Mean (±SD) percentage change in regional lung impedance recorded at maximal inspiration during the forced inspiratory vital capacity (rFIVC) manoeuvre. The oxygen concentration breathed before the hypoxic exposure during which measurements were made is shown. *Significantly ($P < 0.05$) different from baseline (BL)

+Gz exposures, whereas no difference was found after 15 s or for the normoxic 90 s exposure ($P > 0.05$ in both cases). The C_{rs} and R_{rs} did not differ from baseline after any +Gz exposure ($P > 0.05$ in both cases;

Table 1). There was a non-significant tendency for X_{rs} to decrease after the 60 ($P = 0.11$) and 90 s ($P = 0.051$) hyperoxic Gz exposures.

TABLE 1 Respiratory indices recorded after varying durations of Gz (acceleration in the cranial-caudal direction) exposures

Index	Baseline (21% O_2)	15 s	30 s	60 s	90 s	90 s (21% O_2)
FRC_{SF6} slope (log% l^{-1})	−0.188 (0.059)	−0.183 (0.055)	−0.188 (0.053)	−0.192 (0.055)	−0.192 (0.056)	−0.183 (0.049)
FRC_{He} slope (log% l^{-1})	−0.173 (−0.354 to −0.135)	−0.185 (−0.324 to −0.140)	−0.180 (−0.320 to −0.140)	−0.191 (−0.321 to −0.139)	−0.180 (−0.336 to −0.138)	−0.170 (−0.327 to −0.122)
IC (l)	3.86 (0.82)	3.76 (0.690)	3.75 (0.70)	3.49 (0.79)*	3.21 (0.74)*	3.80 (0.69)
ERV (l)	1.57 (0.65)	1.54 (0.68)	1.52 (0.57)	1.46 (0.53)	1.53 (0.66)	1.59 (0.71)
V_T (l)	1.07 (0.47)	1.00 (0.31)	1.11 (0.41)	1.08 (0.37)	1.00 (0.25)	1.30 (0.54)*
f_b (breaths min^{-1})	10.5 (7.2–20.7)	11.6 (9.7–22.4)	12.1 (10.2–20.2)	12.4 (10.9–19.0)	13.0 (10.9–20.2)	12.5 (9.4–22.4)
$\dot{V}_E$ (l min^{-1})	11.7 (3.0)	12.2 (3.5)	13.6 (4.8)	13.9 (4.8)	13.3 (3.6)	16.1 (7.0)*
C_{rs} (l kPa^{-1})	0.194 (0.075)	0.188 (0.048)	0.192 (0.073)	0.171 (0.076)	0.163 (0.051)	0.182 (0.072)
R_{rs} (kPa s l^{-1})	0.399 (0.110)	0.436 (0.107)	0.413 (0.095)	0.420 (0.089)	0.442 (0.086)	0.420 (0.098)
X_{rs} (kPa s l^{-1})	−0.189 (0.076)	−0.182 (0.055)	−0.193 (0.089)	−0.255 (0.0112)	−0.219 (0.086)	−0.208 (0.103)
min S_{pO_2} (%)	91.4 (2.2)	90.8 (2.0)	90.7 (2.9)	90.1 (2.0)*	88.8 (3.0)*	89.6 (3.0)*

Unless otherwise indicated, the oxygen concentration breathed before the hypoxic exposures was 94%. All values are means ± SD except FRC_{He} and f_b, which are the median (range). Abbreviations: C_{rs}, respiratory compliance; ERV, expiratory reserve volume; f_b, breathing frequency; FRC, functional residual capacity; IC, inspiratory capacity; min S_{pO_2}, minimal oxygen saturation recorded during hypoxic period; R_{rs}, respiratory resistance; $\dot{V}_E$, minute volume; V_T, tidal volume; X_{rs}, respiratory reactance.
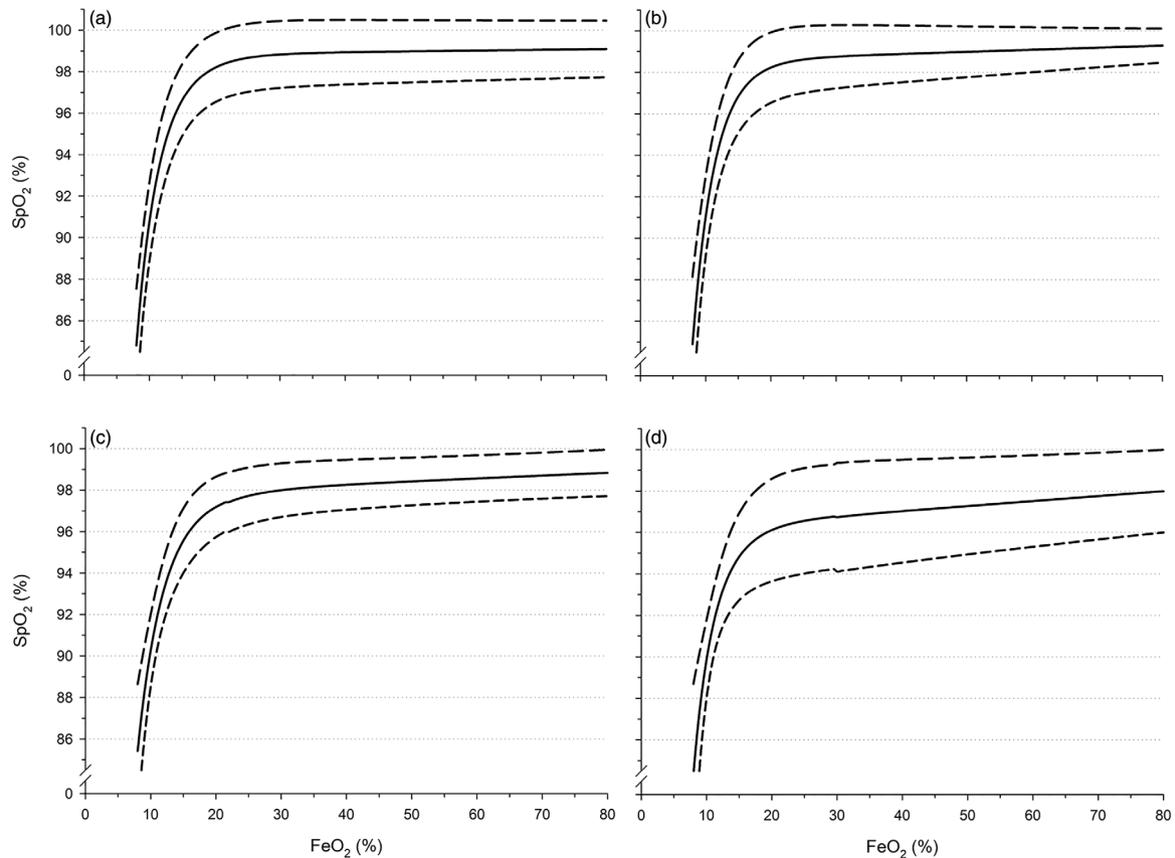*Significant difference from baseline ($P < 0.05$).

FIGURE 4 Plot of oxygen saturation (S_{pO_2}) and end-expiratory oxygen concentration (F_{ET,O_2}) averaged from curves fitted to data obtained after the subjects were switched from the hyperoxic to hypoxic gas mixture after Gz exposures (acceleration in the cranial-caudal direction) of 15 (a), 30 (b), 60 (c) and 90 s (d). Dashed lines indicate the SD

The minimum S_{pO_2} (Table 1) recorded during the hypoxic exposures revealed a significant main effect of the duration of prior +Gz exposure ($F_{5,60} = 6.87$, $P < 0.001$). The degree of hypoxaemia experienced during a hypoxic exposure was found to be exaggerated after 60 ($P = 0.028$) and 90 s (hyperoxic and normoxic; $P = 0.001$ and 0.004, respectively) Gz exposures. There was no difference after 15 and 30 s +Gz exposures ($P > 0.05$). The degree of pulmonary gas exchange limitation present after hyperoxic +Gz exposures was dependent on the duration of exposure ($\chi^2 = 22.16$, $P < 0.001$). No limitation was observed after the 15 and 30 s +Gz exposures, whereas 8.1 ± 1.5 and $12.5 \pm 2.5\%$ were present after the 60 and 90 s exposures, respectively. The level of limitation after both the 60 and 90 s exposures was significantly different from that at 15 s ($P = 0.023$ and 0.002, respectively), whereas there was no difference between the limitation recorded after the 30 and 15 s exposures ($P > 0.05$). The group average S_{pO_2} versus F_{ET,O_2} curve, representing the gas exchange limitation data, is shown in Figure 4.

4 | DISCUSSION

Overall FIVC, rFIVC (measured using electrical impedance tomography), gas exchange limitation and inspiratory capacity, along with self-reported symptoms, were sensitive to acceleration

atelectasis, whereas the forced oscillatory technique and measures of FRC were not. As hypothesized, atelectasis was present after 30 s of +Gz exposure but only when assessed by rFIVC, and the 60 and 90 s exposures revealed the greatest levels of atelectasis. No quantifiable atelectasis was present after 15 s Gz exposures. Reductions in FIVC and IC suggest that significant inspiratory limitation occurs, whereas functional imaging of the lung, using EIT, revealed basal lung closure resulting in gas exchange limitation of up to 12.5%. No evidence of acceleration atelectasis (as determined by measurements of FIVC) was present after the normoxic 90 s exposure while wearing FCAGT, indicating that its development requires high F_{I,O_2} in addition to the use of AGT even with modern anti-G systems.

Although the majority of studies have used +Gz exposures of >180 s to elicit acceleration atelectasis (Borges et al., 2015; Haswell et al., 1986; Hyde et al., 1963), some suggest that 75 s is sufficient (Green, 1963b). The present study supports this, with the majority of individuals developing atelectasis after 60 s exposures. In susceptible individuals, acceleration atelectasis can develop with +Gz durations of 15 s (Glaister, 1965). Overall, no significant effects were noted in the present study after similar durations, although FIVC was reduced by >5% in four subjects, indicating that some individuals might have developed atelectasis. The greater susceptibility of these individuals could be related to breathing at low lung volumes and the resultant lower airway conductance and increased risk of airway

closure at the base of the lung (DuBois, Turaids, Mammen, & Nobrega, 1966) or, possibly, the natural variability in ventilation–perfusion distribution observed in healthy individuals (Baker, McGinn, & Joyce, 1993).

The 10 and 12% reduction in FIVC after the 60 and 90 s exposures is in line with the 10 % reduction noted after breathing 95% O_2 during a 276 s Gz exposure that varied between +3 and 4.5 Gz (Tacker et al., 1987). Although the longer duration of exposures used by Tacker et al. (1987) would typically be expected to elicit a greater degree of acceleration atelectasis, the reason that this is not the case is most probably because of the higher Gz used in the present study, which would have increased pulmonary vascular engorgement, and anti-G trouser inflation, resulting in greater basal lung compression and, subsequently greater development of acceleration atelectasis. Interestingly, using the same Gz exposure as Tacker et al. (1987), it has been found that vital capacity is reduced by 20–30% when breathing 100% O_2 (Haswell et al., 1986), highlighting the importance of considering not only the Gz level but also the F_{I,O_2} when comparing reports of acceleration atelectasis.

When the presence of atelectasis was identified from measures of FIVC, the first FIVC showed the greatest reduction, with normal levels returning by the third. This reversal of atelectasis can be attributed to large changes in intrapleural pressure during the FIVC manoeuvres that re-open collapsed alveoli (Levine & Johnson, 1965). This is in keeping with previous results (Tacker et al., 1987) indicating that the performance of three vital capacity manoeuvres can reverse acceleration atelectasis. Although FIVCs are one of the most common and simplest methods for detecting acceleration atelectasis, it is this reversal process that has driven the need to identify other metrics that can be used to detect formation of atelectasis that are suitable for use in applied research settings.

Imaging of the base of the lung, using EIT, revealed significant reductions in rFIVC not only after 60 and 90 s (hyperoxic) exposures but also after 30 s exposures. The reduction found after 30 s in rFIVC, but not FIVC, suggests that rFIVC might be more sensitive to milder degrees of atelectasis. The greater sensitivity of EIT could be the result of it being measured specifically from the base of the lung, the region most likely to develop acceleration atelectasis, whereas FIVC is a measurement that involves the contribution of the whole lung. Although EIT shows significant promise for assessment of acceleration atelectasis, the method used in the present study (i.e. assessing changes during the FIVC manoeuvre) does not overcome the limitation of performing a breathing manoeuvre. Future studies should explore different electrode placements and the use of higher resolution EIT to allow more detailed imaging of atelectatic regions during and immediately after +Gz exposure.

A non-invasive method for measurement of pulmonary shunt was modified for estimation of the degree of gas exchange limitation from measurements of S_{pO_2} and F_{ET,O_2} (Kjaergaard et al., 2003) made after switching from a hyperoxic to hypoxic gas mixture. After the 60 and 90 s +Gz exposures, a nominal gas exchange limitation of 8.1 and 12.5%, respectively, was found. Previously, (Green, 1963b) measured the degree of pulmonary shunt after a +4 Gz exposure lasting 75 s

while breathing 100% O_2 as 25%. Although not a direct estimate of pulmonary shunt, the techniques used to quantify the data, based on modelling the effects of pulmonary shunt on S_{pO_2} and F_{ET,O_2}, can be compared, in part, with previously recorded shunt data. A slower absorption rate of the breathing gas in the present study (Dale & Rahn, 1952), reducing the extent of alveolar collapse, is likely to explain the lower values recorded. Interestingly, the degree of gas exchange limitation present was sufficient to increase the susceptibility of the subjects to hypoxia, as evidenced by greater hypoxaemia during the hypoxic exposure after 60 and 90 s at +5 Gz. Although this had no detrimental effect on the subjects, if it were to occur during fast jet flight it is possible that it might impair G-tolerance by compounding the hypoxaemia that normally occurs during Gz (Barr, 1962) or increase susceptibility to a subsequent exposure to hypobaric hypoxia (e.g. a rapid cabin depressurization).

The reductions in vital capacity in the present and previous studies (Green & Burgess, 1962; Haswell et al., 1986; Tacker et al., 1987) are primarily attributable to inspiratory reflex limitation (Glaister, 1970; Green & Burgess, 1962). The present data support this contention, given that FIVC and IC were reduced while ERV and FRC were unchanged, indicating an inspiratory limitation. This limitation is likely to be attributable a reduced pulmonary compliance associated with atelectasis (Dellaca et al., 2009; Green, 1963a). In the study by Green (1963a), acceleration atelectasis reduced compliance, as determined from oesophageal pressure measurements, by 17–36% after exposure to 4 Gz for 75 s with F_{I,O_2} of 100%. However, lung compliance, measured using the forced oscillatory technique, was unchanged in the present study, although there was a non-significant tendency for reactance to decline. The lack of a significant change in reactance and compliance might be related to the amplitude of the oscillatory signal used. The mean 1.5 mmHg peak-to-peak amplitude of oscillation was based on a sedated porcine model, in which the forced oscillatory technique was used to detect reductions in compliance associated with atelectasis (Dellaca et al., 2009). It is possible that an amplitude of 1.5 mmHg might not be suitable for seated, conscious humans, in whom it is suggested that an optimal amplitude might be 2.5 mmHg peak to peak (Rotger, Peslin, Farre, & Duvivier, 1991).

Functional residual capacity was unchanged by acceleration atelectasis; however, it is known to decline in response to absorptional atelectasis (Baker et al., 1993). This discrepancy might be attributable to several factors. Firstly, whole-body plethysmography, which has a coefficient of variation of 5% (Quanjer et al., 1993), was previously used to measure FRC (Baker et al., 1993), whereas the inert gas washout technique used in the present study has a coefficient of variation of 12% (Brewer et al., 2011), which prevents small but significant differences being detected. Secondly, the volume of gas trapped in alveoli distal to closed airways under +Gz is unknown, but previous measurements at +3 Gz estimate this to be ~180 ml (Grönkvist, Bergsten, Eiken, & Gustafsson, 2003). Even if it is assumed that all trapped gas is absorbed, the percentage reduction in FRC is likely to be only ~7% (FRC of ~2.4 litres), which might go undetected. Finally, the larger pleural pressure at the base of the lung (Rhoades & Bell, 2013), where acceleration atelectasis is presumed to occur,

ensures that this region provides only a small volume contribution to FRC and ERV (Milic-Emili, Henderson, Dolovich, Trop, & Kaneko, 1966).

An interesting finding was the equivalent change in min S_{pO_2} during the hypoxic exposure after both the normoxic and hyperoxic 90 s exposures, the former occurring without a change in FIVC. This suggests factors other than acceleration atelectasis as the cause and presents the possibility that +Gz *per se* (at least of the durations used here) alters pulmonary gas exchange efficiency. A persisting change in gravitational pulmonary vascular volume is unlikely, and hypoxic pulmonary vasoconstriction would be expected to work in the opposite direction. The finding might be related to alterations in extravascular fluid or transient structural deformation of the lungs and surrounding tissues, although there would need to be further detailed characterization of its resolution before attributing it to this.

The present study is limited by the use of a single acceleration level and oxygen concentration, which are not representative of real flight conditions. Changes in either of these will undoubtedly alter the extent to which acceleration atelectasis develops and, consequently, whether the techniques used can identify it. The acceleration levels and oxygen concentrations were chosen because the study primarily aimed to assess the effect of acceleration duration and the techniques that could be used to monitor development of acceleration atelectasis. Future studies should be conducted to identify the effects of varying oxygen concentrations and acceleration profiles on the development of acceleration atelectasis in settings representative of the modern fast jet flight environment. A limitation on the measurement of FIVC is the time taken after Gz exposure to make this (~7 min), owing to the need for additional measurements to be made before the FIVC so that any reversal of atelectasis as a result of the FIVC does not influence the findings. It is possible that some spontaneous reversal of acceleration atelectasis might have occurred; therefore, the values reported could slightly under-represent the degree of atelectasis present immediately after the exposure. Furthermore, the measurement of FRC required breathing gases with higher than normal concentrations of SF_6 and He. It is possible that the variation in density of these gases relative to air could have altered the regional distribution of ventilation and potentially the extent of development of acceleration atelectasis.

With the estimation of gas exchange limitation, it is important to acknowledge the limitations of the measurement. Although the method used has previously been called a non-invasive estimate of pulmonary shunt (Kjaergaard et al., 2003; Sapsford & Jones, 1995), it is the combination of pulmonary shunt and ventilation–perfusion mismatch that is assessed. Given that one of the greatest effects of acceleration atelectasis would be the development of a pulmonary shunt, the analysis we performed is predominantly based on what would happen to the S_{pO_2} and F_{ET,O_2} with the development of shunt and is therefore not a true measure of gas exchange limitation. Also, by making an individual hypoxic, it is possible that a diffusion limitation could have developed or been exacerbated while also reducing the difference between end-capillary and mixed venous P_{O_2}, potentially influencing the magnitude of any changes observed. Therefore, although the absolute values obtained might vary slightly

between individuals, given that the same protocol was followed after each Gz exposure, the within-subject comparison remains valid. Also, although end-tidal gas measurements are considered a reasonable estimate of the partial pressure in arterial blood, a gradient between the two can exist owing to factors such as dead-space mixing, ventilation–perfusion mismatching and diffusion limitations. Although these factors could influence the absolute measures being made, the comparison between conditions should remain valid.

In summary, this study has provided evidence for the development of acceleration atelectasis after 1 min of exposure to steady +5 Gz in healthy subjects as determined through measurement of FIVC, gas exchange limitation, electrical impedance tomography and subjective measures of symptomology. There does not appear to be any effect of acceleration atelectasis on FRC. The forced oscillatory technique, as used in the present study, has little utility in the assessment of acceleration atelectasis. Our findings indicate that when the primary interest of an investigation is whether acceleration atelectasis develops, measures of FIVC or rFIVC would suffice; however, where greater detail on the physiological consequences of atelectasis is required, these could be supplemented with estimations of gas exchange limitation. Symptoms and inspiratory lung volume limitation attributable to acceleration atelectasis required forced respiratory manoeuvres to allow return of baseline respiratory function.

AUTHOR CONTRIBUTIONS

All testing was conducted at the Farnborough human-carrying centrifuge operated by QinetiQ. R.D.P. and A.T.S. contributed to the design of the work. All authors contributed to the acquisition, analysis or interpretation of the data and to drafting the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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